REMARKS

Claims 1 to 12 appear in this application for the Examiner's review and consideration. There is no issue of new matter.

Claims 1 to 12 were rejected under 35 U.S.C. § 103 for the reasons set forth on page 2 of the Office Action. In particular, the Office states:

> Recrystallization is an age old method for purification.
>
> Recrystallization involves taking the precipitate back into solution and then precipitating it out by change of solubility.
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> This change in solubility can be brought about by a change in temperature or a different solvent. Since Zoledronic acid is an acid it is obvious that as we add a base it would become soluble and dissolve. Thus raising the pH by the addition of a base would dissolve it and then if one would lower the pH it would precipitate out. And this precipitate would be purer than the original acid.
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> Applicants arguments are hence not found to be convincing and the rejection still stands.

In response, Applicants respectfully submit that neither the present Office Action nor the Office Action dated February 22, 2005, cite any reference that supports that statement in the Office Action. In particular, neither Office Action cites any prior art reference that discloses or suggests that a precipitate formed in the presently claimed process of raising the pH of a suspension of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, lowering the pH of the resulting solution until zoledronic acid precipitates out of solution, and isolating the zoledronic acid that precipitates would be any purer than the original zoledronic acid used to form the aqueous suspension. Applicants respectfully request that, if such a prior art reference is known to exist, the reference be cited, and a copy be provided for Applicants review.

Moreover, as discussed in the Amendment filed August 11, 2005, and as required under M.P.E.P. § 2141, neither Office Action provides any reason why one of ordinary skill in the art, at the time the present application was filed, would have a reasonable expectation that zoledronic acid, precipitated with the method of the invention, would be purer than the zoledronic acid originally placed in suspension.

As discussed in the Amendment, filed August 11, 2005, none of the prior art references cited in the Office Action dated February 22, 2005, disclose or suggest anything

regarding zoledronic acid, and none of those references disclose or suggest purifying any material with a process that comprises raising the pH of an aqueous suspension of the material until a clear solution is obtained, lowering the pH of the solution until the material precipitates out of solution, and isolating the precipitated material. Therefore, no reference has been cited for this application that would provide any motivation to one of ordinary skill in the art to purify any material, let alone zoledronic acid, in a process comprising raising the pH of a suspension of an aqueous suspension until a clear solution is obtained, lowering the pH of the resulting solution until a precipitate is formed, and isolating the precipitate. Accordingly, the cited prior art references provide no motivation to obtain the presently claimed process for purifying zoledronic acid.

As none of the cited prior art references disclose or suggest the presently claimed invention, and the cited references provide no motivation for one of ordinary skill in the art to obtain and/or practice the presently claimed invention, the present claims are not obvious over those references.

Moreover, Applicants submit that one of the ordinary skill in the art would not be motivated to obtain and/or practice the presently claimed invention based on what is generally known and available in the pertinent art. In this regard, as discussed in the present specification at page 2, lines 9 to 15, and page 4, lines 28 to 32, the prior art teaches that zoledronic acid can be purified by recrystallization from water, requiring reflux temperatures and large quantities of water. As a result, the required temperature is significantly higher, and the required amount of water is significantly greater than that required in the presently claimed method. As the prior art teaches that zoledronic acid is crystallized from water at high temperature, and does not disclose or suggest the presently claimed process, the prior art provides no motivation for one of ordinary skill in the art to obtain and/or practice the presently claimed invention.

As set forth in M.P.E.P § 2141 (I),

> Patent examiners carry the responsibility of making sure that the standard of patentability enunciated by the Supreme Court and by the Congress is applied in each and every case. The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated:
>
> > Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others,

> etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or non-obviousness, these inquires may have relevancy. . .
>
> This in not to say, however, that there will not be difficulties in applying the nonobviousness test. What is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context. The difficulties, however, are comparable to those encountered daily by the courts in such frames of reference as negligence and scienter, and should be amenable to a case-by-case development. We believe that strict observance of the requirements laid down here will result in that uniformity and definitiveness which Congress called for in the 1952 Act.

Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquires enunciated therein as a background for determining obviousness are as follows:

(A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

Therefore, to establish a *prima facie* case of obviousness, the following are required:

A) A determination of the scope and content of the prior art;

B) An ascertainment of the prior art and the claims in issue;

C) A resolution of the level of ordinary skill in the pertinent art; and

D) An evaluation of the *Graham* secondary considerations.

In the present case, as discussed above, a determination of the scope and contents of the prior shows that the prior art does not disclose or suggest the purification of zoledronic acid with the presently claimed process. Instead, the prior art teaches recrystallizing zoledronic acid in water at reflux temperatures. Applicants submit that there are no known prior art references that disclose or suggest the presently claimed process for purifying zoledronic, and the references cited in the Office Action dated February 22, 2005, fail to disclose or suggest raising the pH of a suspension of an aqueous suspension until a clear solution is obtained, lowering the pH of the resulting solution until precipitation occurs, and isolating the precipitate to purify any material.

An ascertainment of the differences between the prior art and the claims at issue shows the following:

The present claims are directed to a process for purifying zoledronic acid, comprising:

(a) raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained;

(b) lowering the pH of the solution obtained in (a) until zoledronic acid precipitates out of solution; and

(c) isolating the zoledronic acid that has precipitated from the solution in (b).

In contrast, the prior art teaches purifying zoledronic acid using recrystallization in water at reflux temperature. Therefore, the present claims are significantly and patentably different from the prior art.

With regard to the level of ordinary skill in the pertinent art, at the time of the present invention, one of ordinary skill in the art, based on the teachings of the prior art, would have understood that zoledronic acid was purified by recrystallizing the zoledronic acid from water at reflux temperatures. There was no other teaching in the art at that time.

Finally, an evaluation of the secondary considerations shows that, at the time of the present invention, zoledronic acid was purified by recrystallizing the zoledronic from water at reflux temperatures. As a result, the only process known in the prior art requires significantly higher temperatures and significantly greater amounts of water than are required with the presently claimed invention. Reductions in operating temperature and the amount of water required are clearly desirable, particularly in industrial production. However, there is no known prior art disclosure of the purification of zoledronic acid using the presently claimed process. That is, prior to the presently claimed invention, there was an unsolved need to reduce the temperature at which zoledronic acid is purified, and to reduce the amount of water required for the purification, particularly in industrial production. However, prior to the presently claimed invention, such a method was not known or used. This is a clear indication of non-obviousness, as set forth in *Graham*.

Therefore, as the prior art does not disclose or suggest the presently claimed invention, and provides no motivation to one of ordinary skill in the art to obtain the present invention, and there is evidence of secondary considerations that clearly indicate non-obviousness, the present rejection does not meet the requirements of *Graham*, and, thus, the present claims are not obvious. Accordingly, it is respectfully requested that the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

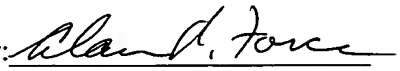
Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

No fee is believed to be due for the filing of this Amendment. Should any fees be due, however, please charge such fees to Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON LLP

Dated: January 20, 2006

By: 

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